Claim 35 (amended) The method of claim 25 wherein the metabolic antioxidnt is lipoic acid, in racemic or enantiomeric form.

Claim 36 (amended) The method of claim 25 wherein the NO synthase inhibitor is a neuronal and/or inductible NO synthase inhibitor.

REMARKS

The amendment is submitted to insert reference to the PCT application and to conform the claims to the American practice.

Respectfully submitted,
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MARKED-UP COPY OF SPECIFICATION

COMBINATION OF NO SYNTHASE INHIBITOR(S) AND METABOLIC ANTIOXIDANT(S)

--This application is a 371 of PCT/FR00/00812 filed March 31, 2000.--

The invention relates to a pharmaceutical composition containing, as active ingredient, one or many substance(s) which interfere(s) with the synthesis of nitrogen monoxide by inhibition of NO synthase and one or many metabolic antioxidant(s) which intervene(s) in the redox status of thiol groups, and optionally a pharmaceutically acceptable support. The invention also relates to a product containing one or many NO synthase inhibitory substance(s) and one or many metabolic antioxidant(s) which intervene(s) in the redox status of thiol groups, as a combination product, in separated form, of these active ingredients.

A pharmaceutical composition and a product according to the invention are useful in the treatment of pathologies where nitrogen monoxide and the metabolism of antioxidants (such as vitamin E or glutathione) as well as the redox status of the thiol groups are involved, and in particular :

. cardiovascular and cerebrovascular disorders comprising, for example, migraine, arterial hypertension, cardiac or cerebral infarctions of ischemic or haemorragic origin, ischemias and thromboses ;

. septic shock, radioactive irradiation, solar radiation, organ transplants ;

. disorders of the central or peripheral nervous system such as, for example, neurodegenerative diseases where cerebral infarctions, senile dementia, including Alzheimer's disease, Huntington's chorea, Parkinson's disease, Creutzfeld-Jacob's disease, prion diseases, amyotrophic lateral sclerosis, but also pain, cerebral or bone marrow traumas, addiction to opiates, alcohol and addictive substances, erective and reproductive disorders, cognitive disorders, encephalopathies, depression, anxiety, schizophrenia, epilepsy, sleeping disorders, eating disorders (anorexia, bulimia, etc.) can be mentioned in particular ;

. proliferative and inflammatory diseases such as, for example, cancer, atherosclerosis, pulmonary hypertension, glomerulonephritis, portal hypertension, cataracts, psoriasis, arthrosis and rhumatoid arthritis, fibroses, amyloidoses, inflammations of the gastrointestinal system (colitis, Crohn's disease) or of the pulmonary system and airways (asthma, sinusitis) as well as contact or delayed hypersensitivities ;

CLAIMS

1. Pharmaceutical composition containing, as active ingredient, one ~~or many~~ NO synthase inhibitory substance(~~s~~) and one ~~or many~~ metabolic antioxidant substance(~~s~~) possessing at least two thiol groups and which intervene(s) in the redox status of thiol groups, and optionally a pharmaceutically acceptable support.

2. Pharmaceutical composition according to claim 1, containing, as active ingredient, a NO synthase inhibitory substance and a metabolic antioxidant substance.

3. Pharmaceutical composition ~~according to one~~ of claims 1 ~~to 2, characterized in that~~ the NO synthase inhibitory substance and the metabolic antioxidant substance are in separated form.

4. Pharmaceutical composition ~~according to one~~ of claims 1 ~~to 3, in which~~ the metabolic antioxidant is dithiothreitol, pyritinol, lipoic acid ~~or~~ its derivatives, the dimeric disulphide derivatives of penicillamine or N-acetylcysteine, ~~or the~~ peptides comprising at least two cysteine residues.

5. Pharmaceutical composition ~~according to one~~ of claims 1 ~~to 2, characterized in that~~ the NO synthase inhibitory substance and the metabolic antioxidant substance are in the form of a salt.

6. Pharmaceutical composition ~~according to~~ claim 5, ~~characterized in that~~ the salt is formed from a derivative of the NO synthase inhibitory substance containing at least one basic group and a derivative of the metabolic antioxidant substance containing at least one acid group.

7. Pharmaceutical composition ~~according to one~~ of claims 5 ~~to 6, in which~~ the metabolic antioxidant is lipoic acid or its derivatives, the dimeric disulphide derivatives of penicillamine or N-acetylcysteine, ~~or the~~ peptides containing at least two cysteine residues.

8. Pharmaceutical composition ~~according to one~~ of ~~the preceding claims, in which~~ the NO synthase inhibitor is a compound of amino acid type, ~~or~~ a compound of the guanidine, isothiourea, nitro- ~~or~~ cyano-aryl, amino-pyridine, ~~or~~ amino-pyrimidine, amidine, indazole ~~or~~ imidazole families.

9. Pharmaceutical composition ~~according to~~ of claim 8 ~~in which~~ the NO synthase inhibitor of amino-acid type is L-arginine, ornithine and lysine derivatives.

10. Pharmaceutical composition ~~according to one~~ of ~~the preceding claims, in which~~ claim 1 wherein the NO synthase inhibitor is ~~chosen from~~ selected from the group consisting of L-nitro-arginine, L-nitro-arginine methyl ester, L-N-monomethylarginine, aminoguanidine, agmatine, 2-amino-1-(methylamino)benzimidazole, 5-nitro-indazole, 6-nitro-indazole, 7-nitro-indazole, 1,2-(trifluoromethylphenyl) imidazole, 2-amino-4-methyl-6-(2-aminoethyl)pyridine, 2-iminopiperidine, 2-iminohomopiperidine, 2-imino-5,6-dihydro-1,3-thiazine, 2-imino-5,6-dihydro-1,3-oxazine, 2-iminotetrahydropyrimidine, N-phenyl-2-thiophenecarboximidamide, S-ethylisothiourea, S-methyl-L-thiocitrulline and S-ethyl-L-thiocitrulline.

11. Pharmaceutical composition ~~according to one~~ of ~~the preceding claims, in which~~ claim 1 wherein the metabolic antioxidant is lipoic acid in racemic or enantiomeric form.

12. Pharmaceutical composition ~~according to one~~ of ~~the preceding claims, in which~~ claim 1 wherein the NO synthase inhibitor is a neuronal and/or inductible NO synthase inhibitor.

13. Product containing one or many NO synthase inhibitory substance(s) and one or many metabolic antioxidant substance(s) possessing at least two thiol groups and which intervene(s) in the redox status of thiol groups, as combination product in separated form, for simultaneous or sequential use in the treatment of pathologies in which nitrogen monoxide and the redox status of thiol groups are involved.

14. Product according to claim 13 for the treatment of pathologies such as cardiovascular and cerebrovascular disorders, septic shock, radioactive irradiation, solar radiation, organ transplants, disorders of the central or peripheral nervous system and more particularly Parkinson's disease, proliferative and inflammatory diseases, autoimmune and viral diseases, diabetes and its complications, autosomal genetic diseases and all the pathologies characterized by a production or a dysfunction of nitrogen monoxide and/or involving the redox status of thiol groups.

15. Product according to claim 14, for the treatment of cerebrovascular and cardiovascular disorders such as migraine, arterial hypertension, cardiac or cerebral infarctions of ischemic or haemorragic origin, ischemias and thromboses.

16. Product according to claim 14, for the treatment of disorders of the central or peripheral nervous system such as neurodegenerative diseases, and more particularly Parkinson's disease, pain, cerebral or bone marrow traumas, addiction to opiates,